# Modes of Inheritance

## Inheritance Patterns

Our goal here is to help identify **simple modes of inherence.** Simple means the disease is present or it isn't. The next lesson grapples with inheritance patters on a much deeper level. Some resources use the term "Mendelian inheritance." We'll explain inheritance patterns, but the large focus (here and on the test) is on **pattern recognition in pedigrees**—being able to determine the inheritance pattern without deducing anything—follow the rules to win the day. After that, we'll explain how to determine **recurrence risk** and identify **obligate carriers**. And that's the tricky part.

## How Genes Are Passed On

There are **three** main types of inheritance: autosomal, X-linked, and mitochondrial.

The **autosomal** pattern means that any of the non-sex chromosomes may carry the gene of interest. Because all organisms have two sets of autosomal chromosomes, autosomal genetic disorders are sex-agnostic. Both sexes are affectedly equally in autosomal inheritance patterns. That means a male-to-male transmission must be autosomal.

**X-linked** disorders are, by their nature, on the X chromosome. Because men have only one X chromosome, they're more vulnerable to expression. Regardless of whether the bad copy is dominant or recessive, males only get one copy, period. So, inheritance patterns that **mostly affect males** could be X-linked. However, the most important feature of X-linked transmission is that because the male has only one X chromosome, he can pass on the X chromosome only to his daughters—**any male-to-male transmission** guarantees that the inheritance is **not X-linked**.

**Mitochondrial** inheritance must be mother-to-child only—all of mom's mitochondrial DNA goes into her egg, so all of an organism's mitochondrial DNA is from mom. Which means that **mothers** with a mitochondrial inheritance disorder **must pass it on to all of their offspring**, while affected fathers will never pass it on.

## Dominant vs. Recessive

**Dominant.** Every gene should have two good copies. In a disease that's inherited from a dominant allele, **one bad copy** means disease. Dominant inheritance means that **every generation is affected**. This must be the case—if the gene is present in an organism, it'll have the disease. If it's in an organism it will be passed down.

**Recessive**. Every gene should have two good copies. Only one good gene is needed to prevent disease. If both copies of a good allele are bad, disease results. Two copies of the good genes means no disease. An organism with one good gene and one bad gene **doesn't** have the disease but is a **carrier**—it can pass that disease on to its offspring.

## Pedigree Patterns

Pedigrees are assessments of individuals in a family. The test will present a pedigree and ask for the inheritance type. Squares are males, circles are females. Darkened shapes are affected, lightened shapes are unaffected. Affected means "shows disease." Depending on the inheritance pattern, "affected" implies different things about the genotype of the individuals.

## Punnett Squares and Recurrence Risk

We are assuming there will ever be only two variations of an allele, and each individual parent has two copies of an allele. When two people mate, they can have four combinations of alleles. Since each gamete will contain only half of the genetic code from each parent, and the parents' offspring will be a combination of those gametes, the potential combinations can be represented by a Punnett square. Each quadrant represents a different potential outcome. When calculating recurrence risk, we determine how many of the four boxes satisfy the criteria for the assessment. The number of squares divided by 4 will give the answer. "The criteria for assessment" could be anything—affected, unaffected, carrier states . . . you'll have to interpret the givens and populate the square to get the answer.

## Autosomal Dominant

Autosomal—**both sexes affected equally**; dominant—**present in all generations**. Autosomal dominant requires that only one bad copy of the gene be present to result in disease. This means there's a **fifty percent chance** that any affected parent will pass the disease on to their offspring. There isn't a carrier state.

It's difficult to assess whether a disease is homozygous or heterozygous. The way we're considering things, the affected person could be affected either way. When asked to do recurrence risk, assume heterozygous, unless it's certain that the affected person with an autosomal dominant disease is homozygous. At this point, the goal isn't to employ tricky, weird percent-chances like in undergrad, it's to identify the pattern.

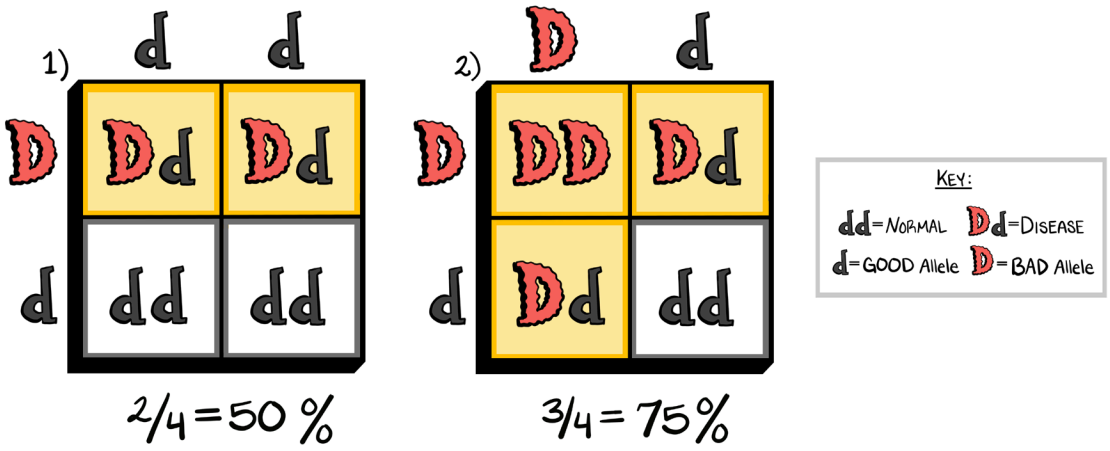


**Figure 2.1: Recurrence Risk in Autosomal Dominant**
1) If an affected person (one good, one bad allele) mates with an unaffected person (both good alleles), there is a 50% chance that the affected person will pass on the one bad gene, and so a 50% recurrence.
2) If two affected people (each with one good, one bad allele) mate, then any permutation that has any one bad gene will be affected, meaning there is a 75% chance of recurrence.

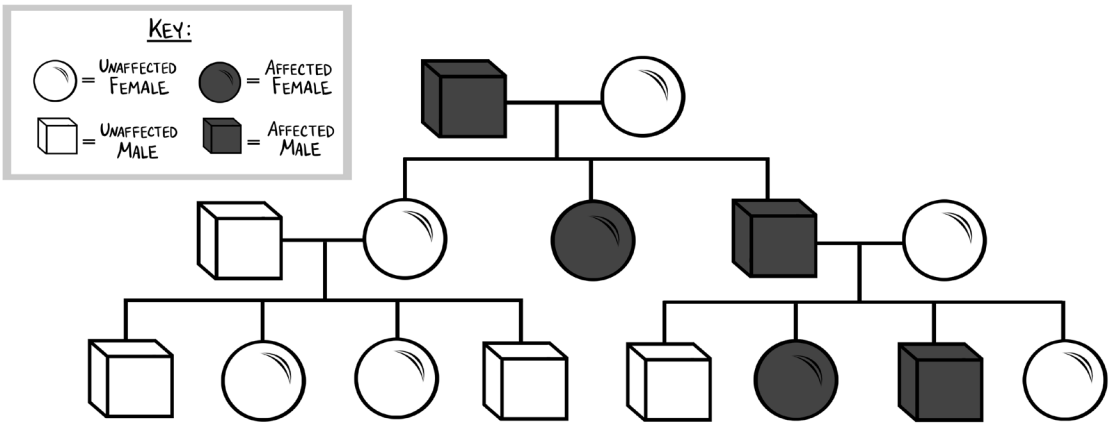


**Figure 2.2: Autosomal Dominant Pedigree**
All generations and all sexes affected. Another tip-off is the sheer number of people affected.

## Autosomal Recessive

Autosomal—**both sexes affected equally**; recessive—**skips generations**. Recessive alleles are responsible for loss-of-function variations that necessitate two bad copies to express disease. This means that individuals can have a copy of the bad allele without expressing any disease, a state called the **carrier state**. The expression of these diseases is rare because the disease can present only when two carriers mate (good_bad x good_bad) AND they get an unlucky pairing of bad_bad. But the carrier state can linger, because by itself, it causes no disease.

That means the number of affected individuals will be low. **Pedigrees without many individuals** or **those that skip generations** are likely to be autosomal recessive.

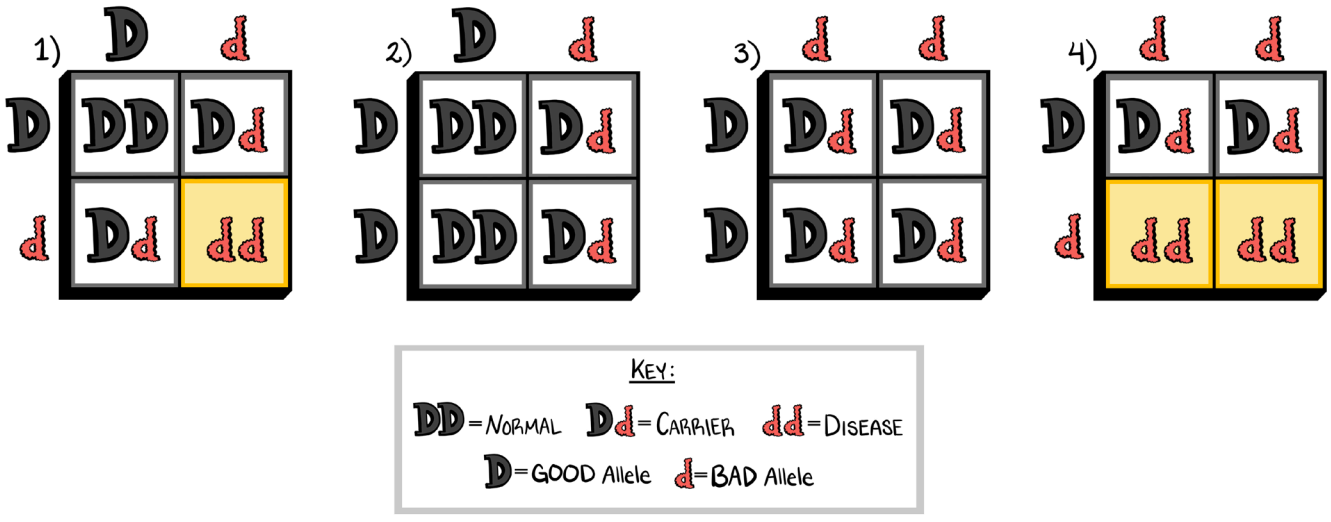


**Figure 2.3: Autosomal Recessive Possible Mating Outcomes**
1) Two carriers mating (this must be the case if a couple has one affected child with an autosomal recessive disease) have a 25% chance of recurrence. 2) A homozygous normal can't have an affected child, 3) even if the mate is homozygous diseased; 4) but a carrier and an affected have an increased risk of recurrence, but only to 50%. Recessive disorders are hard to express.

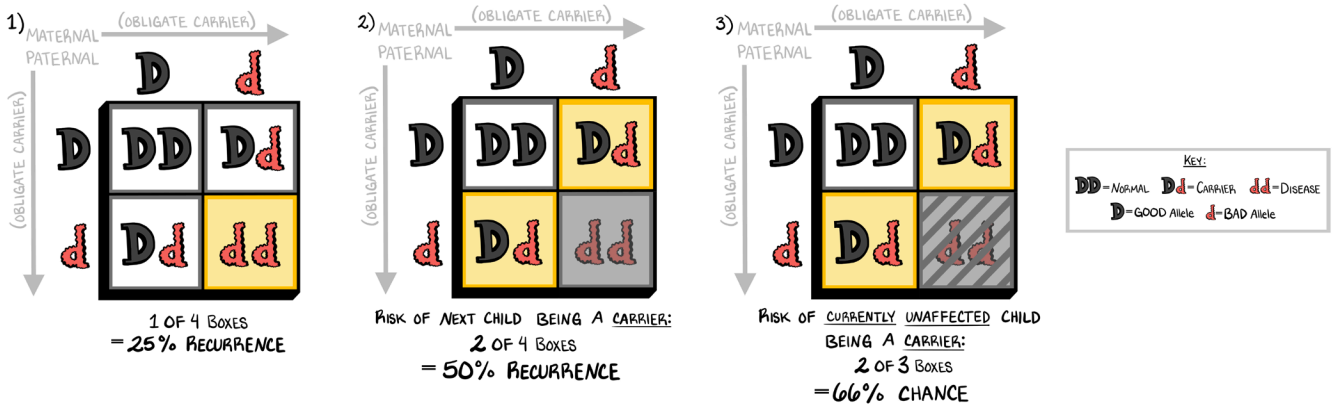


**Figure 2.4: Recurrence Risk in Autosomal Recessive**
Read the test questions carefully: If they ask the risk of 1) a couple having another affected child, the answer is 25%. If they ask the risk of 2) the next child being a carrier, the answer is 50%. If they ask the chance of 3) the unaffected child in front of you, sibling of an affected child, being a carrier, the answer is 66%.

Both parents of an affected child must be **obligate carriers** if an autosomal recessive disorder is ever expressed. Neither parent is affected—this alone means they could be either homozygous normal or heterozygous carriers—and their child has two bad alleles: two bad copies, one from each parent—so therefore both must have had at least one copy of the bad gene, narrowing both of their genotypes to be a heterozygous carrier. And if they have one child with the autosomal recessive pairing, that means that they're capable of having another. By necessity, an individual with an autosomal recessive disorder has two carrier parents, 25% of whose offspring will have been affected. **Recurrence risk** is therefore **25%** for any couple that has a child with an autosomal recessive disease but are not affected themselves.

The recurrence risk for the next child to be affected by two obligate carriers (a couple that has had an affected child) is 25%. But different questions can be asked about the same couple. If they ask the chance of the next child being a **carrier**, the answer is **50%** (2 of 4 boxes). If they ask what is the chance that a living child showing no evidence of a syndrome (i.e., the dd box is eliminated) is a carrier, the answer is **2/3** or **66%.**

If an affected individual is able to live and reproduce (many autosomal recessive diseases are fatal or limit reproduction), then that person will hand down the bad gene **100%** of the time. This means offspring become at least carriers, and you can see affected individuals. Not likely to be seen on the test, but the square needs to be carefully constructed.

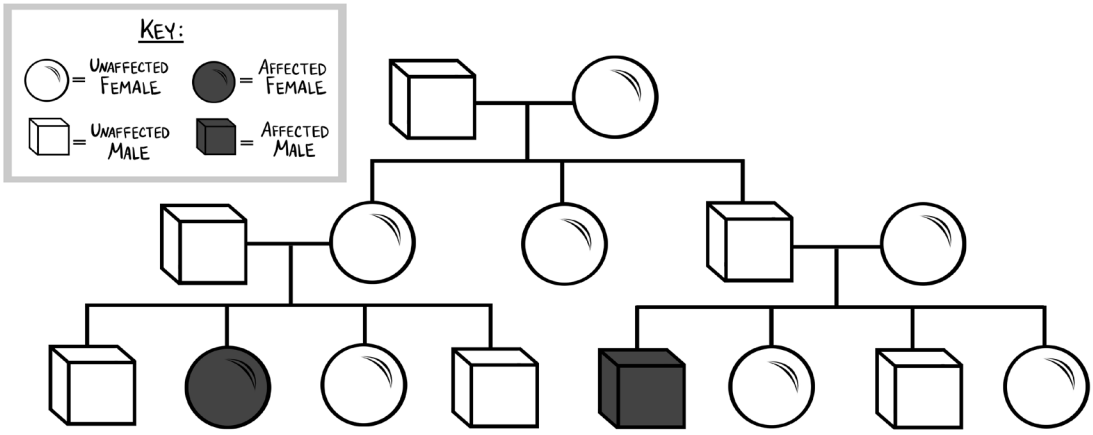


**Figure 2.5: Autosomal Recessive Pedigree**
Almost no affected individuals, male-to-male transfer, generations skipped or unaffected.

## X-Linked Recessive

ANY **male-to-male transmissions RULE OUT X-linked disorders**. There'll be skipped generations (it's recessive): for example, an affected father passes on a bad X to his daughter, while the mother passes on a good one. Females can be affected. However, more than likely the pedigree will show **only males affected.**

**Obligate carrier** is a nice question to ask about X-linked recessive. **Both** the **mothers of affected sons** and the **daughters of affected males** must be at least an **obligate carrier**. To have a son that has the disease, the mother must be the one to carry the bad X. The affected male (who has only the bad X) must give that X to his daughters. It's possible to have an affected female—the daughter of an affected male paired with a carrier (thereby ensuring that the **mother of an affected daughter is an obligate carrier**)—though this is unrealistic, as many X-linked recessive disorders result in sterility or early death. Still, the obligate carrier state becomes the preferred way the test goes after X-linked recessive.

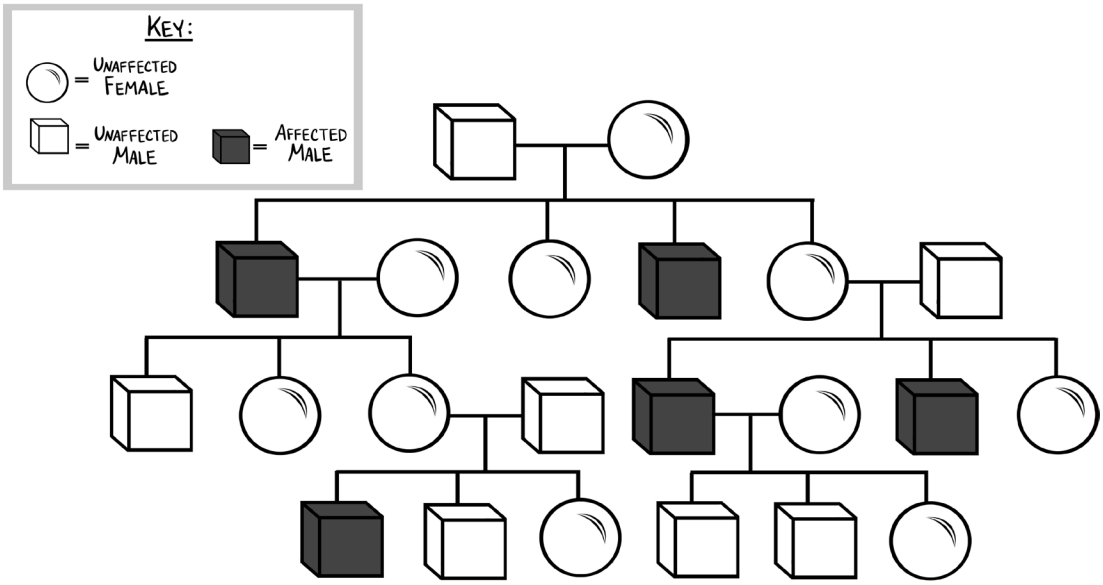


**Figure 2.6: X-Linked Recessive Pedigree**
Only males, no male-to-male transmission, skips generations.

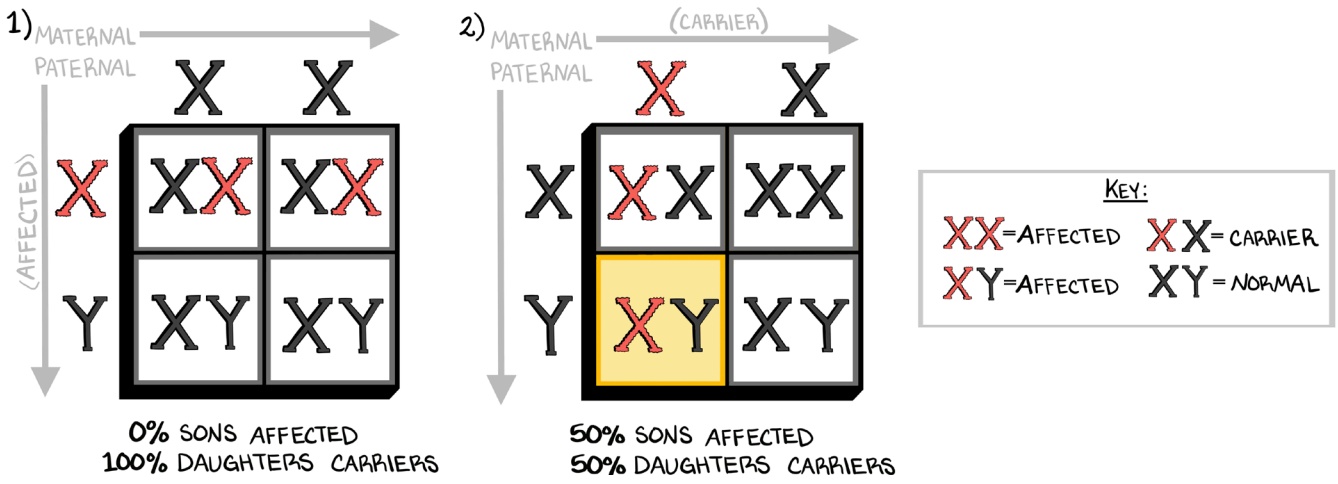


**Figure 2.7: Recurrence Risk with X-Linked Recessive**
1) If the father is affected, he cannot pass on any X genes to his sons, and all of his daughters will be at least carriers. 2) If the mother is a carrier, only her sons can be affected, 50% of her sons will be affected, and 50% of her daughters will be carriers.

The recurrence risk of an X-linked recessive disorder most often will come from the female carrier state with a normal male. Since the male passes on the Y, only the female determines diseases—half of a female carrier's sons will be affected.

## X-Linked Dominant

It's **dominant—every generation is affected**. It's **X-linked**, meaning there can be **no male-to-male transference**. But, unlike recessive, now the **affected female state** is quite possible. It doesn't matter that she has a good X chromosome. If she has just one bad one, she's left with the disease.

An affected male is known to have the bad allele. An affected female provides no information about her genotype. The affected female may be either homozygous-disease or heterozygous. When doing **recurrence risk**, always assume that the affected mother is a **heterozygote—**unless it's certain that she's a homozygous X-linked dominant.

If the mother is heterozygote-affected, then she'll pass on her bad X to **both males and females,** but only **half the time**. Mothers are sex-neutral, but pass on the bad gene half the time, and the good gene the other half the time. Recurrence risk for a mother-affected-X-linked-dominant is 50% offspring, 50% girls, 50% boys.

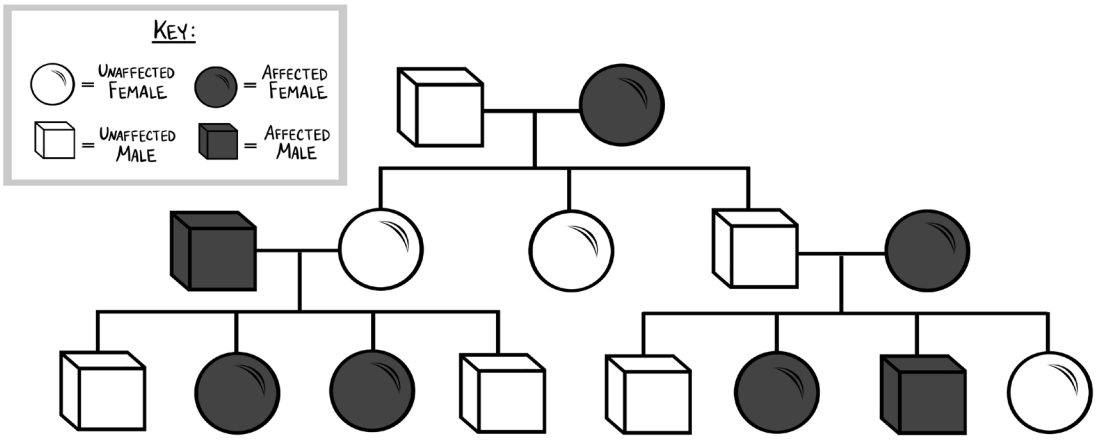


**Figure 2.8: X-Linked Dominant Pedigree**
Both males and females, every generation, no male-to-male transfer.

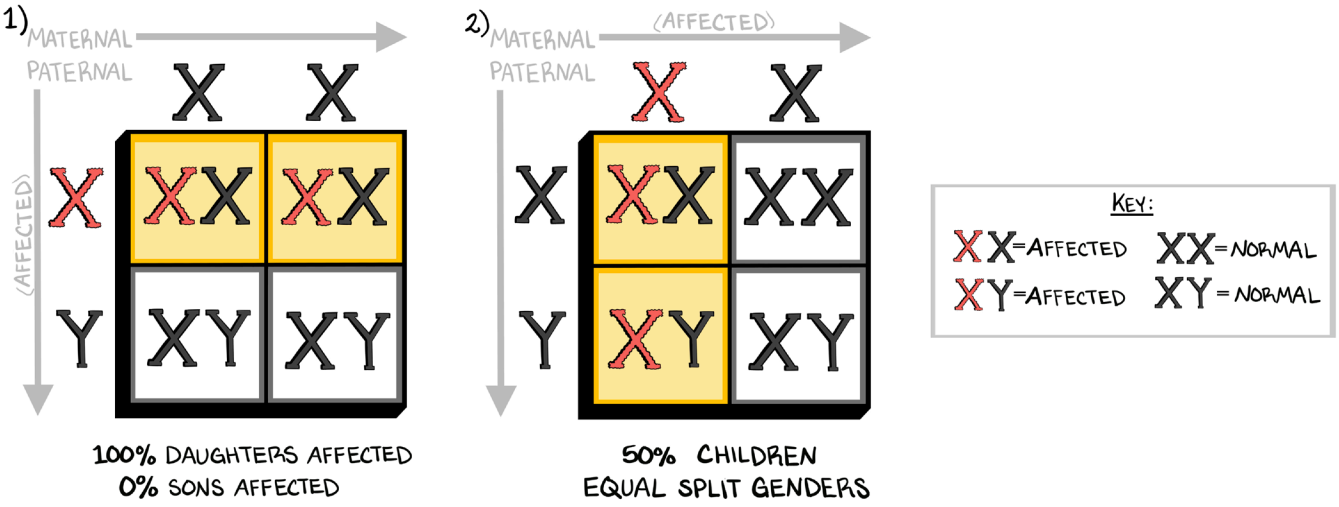


**Figure 2.9: Recurrence Risk, X-Linked Dominant**
1) If the father is affected, he will pass the disease to 100% of his daughters, but cannot pass it to any of his sons. 2) If the mother is affected, she will pass the disease to 50% of her children, with equal split between sexes.

If the mother is normal, and the father is affected, he's **guaranteed to give a bad X**, but only **half the time**. He'll give none of his sons the disease (receiving his Y instead), though he'll give all his daughters the disease (receiving his bad X). Recurrence risk of a father-affected-X-linked-dominant is 50% offspring, 100% girls, 0% boys.

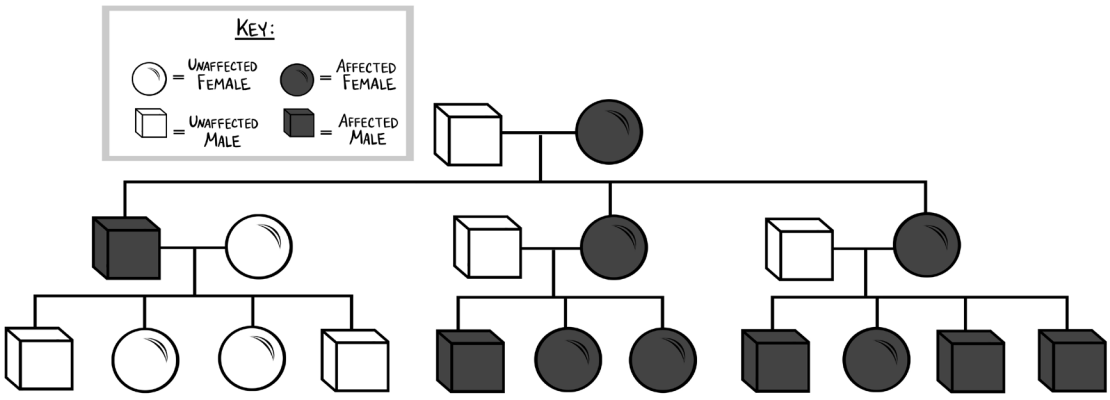


**Figure 2.10: Mitochondrial Inheritance**
All children of an affected mother are affected.

## Mitochondrial Inheritance

This is easy to spot. No father passes on the disease to any child because mitochondria come from mom's cells. There isn't a sharing or a pairing—**all mitochondrial DNA comes from mom**, and therefore **all children of an affected mother are affected.**